Editor's Comments to the Author:  
Subject Editor: 1  
Comments to Author :  
Two very positive sets of reveiwers' commenst; please consider these as I believe that they improve clarity.  I am delighted, otherwise, to recommend acceptance.  
  
Reviewer(s)' Comments to Author:  
  
Reviewer: 1  
  
Comments to the Author  
In this manuscript, the authors sought to elucidate the impact of climate change (and other abiotic and biotic predictors) on plague distribution and risk and determine if spillover risk has changed since 1950. They found that rodent communities, soil biochemistry, and climate change have all influenced plague distribution and disease risk, and that spillover risk has increased over time.  
  
This manuscript is well-written and easy to understand. The ecological insights seem sound and the authors do a good job of explaining the potential impact of each variable on plague persistence and infection risk.  
  
I am not experienced in some of the methods used here. In particular, I was not able to review the specific methodology related to the CART, BART, and riBART methods (Lines 512-548, 558-582, 613-619, and 635-684). However, even without fully understanding the specific statistical methods behind the regression trees, I was still able to easily follow the results and discussion.

We appreciate the positive feedback!

I suggest no major revisions and I have no major concerns. I do have smaller suggestions that are aimed to improve the readability and make it easier for non-experts in the field to understand.

Introduction:  
I would add a sentence or two to the introduction about the life cycle of the bacteria. I would detail how it uses the soil, fleas, and vertebrate hosts, how it moves between them, and that susceptibility and suitability varies across hosts and how this impacts human risk. It would fit well before the paragraphs starting at lines 93 and 112.

We appreciate this suggestion, and have added a fully referenced paragraph that starts at the location on line 93 to include additional information on the bacterium's life cycle:

“Few systems provide a better opportunity to test this approach than plague, a globally-cosmopolitan zoonotic infection caused by the bacterium *Yersinia pestis*. The bacterium is typically maintained by rodent (and sometimes shrew) hosts and the fleas that live on them or in their nests. Suitable plague reservoir host species are often thought to exhibit a standing variation in their susceptibility to the bacterium, such that some hosts generate a high enough (and often lethal) bacteremia in the blood for the efficient transmission of the bacterium by flea vectors, while the host population as a whole survives. Which local flea species are important for the spread and persistence of the pathogen depends on their typical host's abundance, and the taxonomic range of hosts that they feed upon; both of these factors are correlated with intrinsic variation in their vector competence, and have important implications for plague dynamics, including spillover risk for humans. While other transmission modes are sometimes relevant to both spillover and epidemic transmission, including consumption of infected meat and droplet transmission respectively, the relationship between rodents, fleas, and bacteria gives shape to most salient ecological questions.”  
  
Line 59: “While there are substantial research efforts working to project these future changes” – I would add one or a few citations as examples.

We appreciate this point and have added three relevant citations at this location

Lines 118-119: Please define early-phase transmission and blockage-induced transmission.

The two terms are not easily captured in short definitions, and while there are interesting points where this intersects with the subject of our manuscript, the distinction is largely irrelevant, so we have removed this passage.

Line 124: “Finally, temperature also influences” rather than “Temperature also finally influences”

We have made the suggested change.

Line 135: Add “(USDA)” after U.S. Department of Agriculture

We have made the suggested change.

Results:  
One difficulty with journal formats that put the methods after the results and discussion is the lack of knowledge of the specific details when moving into the results and discussion. With this layout, I would reiterate some of the method details in the results so the reader doesn’t constantly have to flip between the methods and the above text when reading through the paper. A little bit of repetition by the time you get to the methods is preferable to the constant jumping. Some examples of this:  
Line 163: “animals” – what kinds? Maybe a list of orders or numbers of family represented  
Line 327: A quick explanation of how the diagnostics changed would be useful here  
Line 406: Define PRISM and add citation

We appreciate these points and have decided to move the Methods up before the Results as the most direct possible solution to this problem.

Line 260: Specify Celsius

We have made the suggested change.

Lines 261-262: Please provide a short explanation of this empirical work. Does this temperature range match higher NA flea abundance or diversity? For the Third Pandemic spread, was the largest number of human cases at this temperature range? Was there higher risk at this range?

We updated the below paragraph to be more specific on the empirical work, both for the wildlife and the human model. While doing so we decided that the Third pandemic reference was better replaced by a more extended description of the empirical work, due to some methodological issues in the citation (which, on closer inspection, treats any local introduction of plague as though it were permanently capable of being a source of subsequent outbreaks, regardless of whether plague was actually documented to persist at that locale).

Our rewritten section now explains:

“In the wildlife model, we found a loose peak around 7C but overall a negative relationship between mean temperature and plague risk--an unusual response curve for a vector-borne disease. In the human model, risk is highest around a mean temperature of 11C, and suitability increases steeply above a maximum temperature of 10C but stabilizing around 25C. Despite some unusual features, these results are broadly consistent with prior experimental work on *Oropsylla montana* and *Xenopsylla cheopis* respectively, two of the main plague vectors in North America. Lemon *et al.* report that a significantly larger fraction of *O. montana* become infected with plague when feeding on an infected blood source at 10C than at 21C; Williams *et al.* similarly report a peak transmission rate for *O. montana* at 10C across a temperature range from 6--23C. In contrast, the survival rate of infected *X. cheopis* is markedly higher at 21C compared to 10C, and the highest plague transmission efficiency is observed at 23C. In addition to vector competence, many other factors of plague risk are temperature sensitive, from the straightforward (e.g., flea infestation levels) to the more abstract (e.g., some colder temperature ranges may characterize the rural areas in the Rocky Mountains where people live alongside plague reservoirs). Disentangling these factors may shed further light on the more unusual aspects of the thermal response curves we identified.”

Lines 300-301: Please define/provide an explanation for fractional CO2 and atmospheric fraction.

This is now clarified as “with a 100-fold higher level of CO2 (as a fraction of total molecules in the air) than the atmospheric fraction”

Discussion:  
Lines 349-350: A brief reminder about what these hypotheses are would be helpful.

We now explain: “We found support for two major hypotheses: the biodiversity amplification effect (higher rodent diversity supports establishment of plague foci) and the trophic cascade hypothesis (anomalously warm or anomalously wet, cold years can increase plague prevalence and spillover risk respectively, through ripple effects of ecosystem productivity on rodents and flea populations).”

Line 374: “It may also likely reflects” – awkward wording

We appreciate this point and have rephrased to read “It may also reflect concerns…”

Line 379: I would reiterate that you’re talking about the borders of the US (“national US borders”). Much of this paragraph is global in scope, so it’s not obvious when reading this that you’re talking about the US borders until you see Mexico and Canada a few lines down.

We have rephrased this to read “…that wildlife reservoirs extend to the U.S. borders with both Mexico and Canada…”

Lines 386-388: These two methodological advances are a big selling point, and I might highlight them in the abstract (even briefly).

We appreciate this suggestion and have rephrased the abstract as such:

“Here, we test whether animal and human data suggest that plague reservoirs and spillover risk have shifted since 1950. To do so, we develop a new method for detecting the impact of climate change on infectious disease distributions, capable of disentangling long-term trends (signal) and interannual variation in both weather and sampling (noise).”

Methods:  
General: Please cite R packages and include in-text citations.

We appreciate this suggestion (particularly as software developers!) and we have added the appropriate citations for all R packages now.

Lines 440-441: Either define the different plague types here or provide this information briefly in the introduction when you give background on Y. pestis.

We appreciate this suggestion and have added an explanation:

“Human cases of plague occur sporadically but consistently in the Western United States, driven partially by exposure to infected cats and dogs that have acquired the infection out-side of the home. The vast majority of the human cases in the United States are infected with the bacterium through flea bites, which typically leads to bubonic plague if the infection is deposited into the skin tissue and results in an infection of the lymphatic system, or (less commonly rarely) as septicemic plague if the infection is deposited in the blood stream. In only about 3% of the human cases, the disease manifests as pneumonic plague, when the infection was acquired by inhaling infectious droplets coughed up by infected animals or humans.”

Lines 463-464: Please provide more information about the animals sampled. How many other species are represented? From what orders? Can you give a % breakdown by order? Is prevalence in coyotes directly proportional to prevalence in rodents and/or fleas?

We appreciate this suggestion and have added the following sentence to the methods section on wildlife serology data (lines 463-464) to provide more detail on the animal samples:

“In total, the version of the dataset we used spanned February 13, 2000 to January 29, 2018, with a total of 41,010 records, including 5,043 animals that tested positive. Of those records, the vast majority are coyotes (32,825 animals including 4,812 that tested positive). Species from the order Carnivora make up 92% of the dataset, followed by Rodentia (6%), and the remaining came from a variety of taxonomic groups (Artiodactyla, Lagomorpha, Didelphimorphia, Cingulata, and Eulipotyphla). The most commonly tested rodents were beavers (*Castor canadensis*; n = 1,609), nutrias (*Myocastor coypus*; n = 204), and muskrats (*Ondatra zibethicus*; n = 94).”

Prevalence in predator species is not always directly proportional to plague prevalence in rodents or fleas, although work has shown increased prevalence in coyotes can precede human exposures (see https://www.liebertpub.com/doi/full/10.1089/vbz.2010.0196).

Line 505: Cite IUCN range map data.  
  
Figures/Supplemental Material:  
For all multi-plot figures, I would add column and row headings for human and wildlife maps, especially since this changes (sometimes humans are in the left column, sometimes they’re on the top row).

We appreciate this suggestion and have made this change in all main text figures.  
  
Figure 3: It is difficult to see changes in suitability between the left and right columns. I would either add or replace these with another two maps that show change between the suitability maps (with and without random intercepts) for wildlife and human models (e.g., darker colors show where suitability is different between the intercept models, lighter colors show where suitability did not change).

While we appreciate this suggestion, there are two reasons we did not do so in the original manuscript. The first is mostly practical: readers may see another difference manuscript and become confused about whether those differences indicate change over time (i.e. interpret the difference-of-differences as the actual differences). The second is more epistemological: the two models, trained on different baselines (because the random intercept is fit in parallel to the classification trees), make predictions on the same scale but should not be directly compared over space.

Supplemental Figures 7, 9, 22, 25: A little bit of an explanation of how to interpret this would be helpful. I only recently started using GAMs and these plots, but before that I would have been lost.

To each figure caption we have now added: “Partial dependence plots represent the relationship of a single variable to the predicted outcome, on a scale of 0 to 1, independent of the other variables fit in the model; blue shading gives a 95% credible interval from the posterior distribution of the Bayesian model. The steepness of these curves indicates the predicted magnitude of the effect, but not necessarily the variable's importance in the model.”

Supplemental Figure 8: Here as well, an explanation of how to interpret this would be helpful.

We have added: “Brighter colors (yellow) indicate a higher suitability for plague in that part of parameter space. Soils that are mostly sand, with some clay and minimal silt, are most suitable.”

Supplemental Figures 10, 11: Please provide an explanation of what the color scale shows. What do warmer colors and cooler colors mean? You might consider adding labels to the color gradient.

For both, we have added: “Values are unitless partial effects on predicted probabilities that range from 0 to 1.”

Supplemental Figure 12: Why is the soil pH not on a scale of 0 to 14?

We appreciate the eagle-eyed spot here, and have now corrected an error where the axes were missing decimal points (“5.0” represented as “50”)

General: In the text, supplemental information is referred to as “Extended Data Table/Figure” but as “Supplemental Table/Figure” in the supplemental information. I don’t know the requirements of the journal, but it seems like this should match. It makes correlating between the two a bit difficult.

Apologies for the error; this is now fixed.

Reviewer: 2  
  
Comments to the Author  
I enjoyed reviewing this manuscript and appreciate the thought and work that went into exploring plague risk associated with climate change. I think this is valuable science and look forward to more exploration of the ideas, models, and methods put forth here. I ask that the editor and authors read my review keeping in mind that the specifics of modeling are outside my areas of expertise. I have posed questions that came up for me as someone with a mammalogy background and a lot of familiarity with zoonotic research.  
  
There is a relevant body of literature about how climate impacts the the spillover potential of other zoonoses, in particular, the retrospective work on Hantavirus and El Niño in the Four Corners comes to mind. The Hantavirus research is also relevant because it leverages an often over-looked resource for detecting wildlife pathogens, natural history collections. While these resources would not be useful for detecting antibodies (as was done here), they can be screened for pathogen presence. This would be helpful for further refining model predictions by including samples of a broader array of potential wild mammal reservoirs. To be clear, I am not suggestion these data be included in this manuscript, but that it would be a useful direction for future work.

We appreciate this suggestion and entirely agree – this is somewhere that we are hopeful that the Verena Consortium (viralemergence.org) will be working in the next few years.

I have minor comments and suggestions for further exploring or contextualizing the findings.  
  
Lines 180-183: There are some great points about why the models may disagree, but is one of them also just variation in the likelihood human-wildlife contact? Would it be useful to map human population densities?

We appreciate these suggestions and indeed both human-wildlife contact rates and population density are likely to interact with the relationship between suitability and spillover. However, the two are separate processes, and the relationship between them is not straightforward. For a system like plague with an enzootic cycle in wild animals, the relevant overlaps may be higher in more rural areas, leading to a nonlinearity between human population density and actual spillover rates. For this reason, simply presenting a map of population density may lead a reader to spurious conclusions about where risk is highest, and it would be preferable to include human populations in the models directly—and indeed, we did this in the first version of the models we built. However, the spatial autocorrelation between population density and spillover *incidence* becomes a problem for model fitting, because (even log-transformed) human population density varies so much between counties that a spurious positive relationship drowns out the rest of the model (and produces the strongest predictions, unsurprisingly, in the middle of dense metropolitan Los Angeles).

Also, I would think it would vary by the mammal plague reservoir, potentially by the specific rodent species instead of rodent species richness. Humans are much more likely to be close to some populations of wild mammal reservoirs than others. I'm thinking of urban or peri-urban species (e.g., rats, fox squirrels, and prairie dogs) compared to other species that tend to stay away from large human population centers (marmots and chipmunks). Accounting for variation among plague reservoir species may lead to over-fitting problems, but it seems worth considering. These considerations also support the higher potential for spillover noted lines 194-195.

Lines 230-249: This is a helpful discussion of the role of species richness and speaks to the complex dynamics of zoonoses with a broad host range. It would be nice to see more discussion (in the Discussion) of how the presence/absence or richness of synanthropic species might complicate model predictions - particularly given the findings regarding the biodiversity amplification effect.

We appreciate these suggestions, and now better explain both the directions for future research and the complexity that prevented us from addressing these issues in greater depth in this study:

“Support for these patterns has increasingly been found across systems, and points to a view of plague risk where weather conditions (and their impact on flea vectors) in rodent biodiversity hotspots are the primary driver of transmission and spillover. Though the plague ``niche'' may largely transcend any individual host species, in the future, our understanding of these mechanisms might be further refined by exploring more granular variation among the species involved. For example, the amplification effect could be explained by the null hypothesis that higher richness simply represents a higher probability of a few key maintenance hosts being present. Identifying ``true reservoirs'' is a non-trivial task in disease ecology; *Yersinia pestis* can infect hundreds of rodent species, and some species once considered key to maintain endemic plague are now known to be spillover hosts from unknown reservoirs. Rodent habitat use adds another dimension to the problem: synanthropic and ``wild'' reservoirs may have very different richness hotspots, which may explain some differences between the geography of maintenance and spillover (as, alternately, could the geography of domestic cat and dog ownership). These patterns are further complicated by potential variation among fleas, with over two dozen experimentally-verified vectors in the United States alone, which vary in geographic distribution, thermal sensitivity, and affinity for wildlife and human hosts. All of these nuances may point to promising directions for future data synthesis and modeling.”

Line 379: The use of the word "up" is confusing, in my mind only the Canadian border is "up". I suggest re-wording to "extend to both national borders."

We have rephrased this to read “…that wildlife reservoirs extend to the U.S. borders with both Mexico and Canada…”

Lines 462-464: I think it would be helpful if the authors would include the number of species, particularly rodents, that were tested. Given that the model is using rodent species richness, I would like to know how many rodents are included in the serology dataset. Taking it even further, a supplemental table of the sample sizes and species sampled would be of interest to some readers.

The dataset includes 90+ distinct species entries, as well as a number of records only resolved to the level of genus, so a supplementary table may be impractical. However, we now state in the methods:

“In total, the version of the dataset we used spanned February 13, 2000 to January 29, 2018, with a total of 41,010 records, including 5,043 animals that tested positive. Of those records, the vast majority are coyotes (32,825 animals including 4,812 that tested positive). Species from the order Carnivora make up 92% of the dataset, followed by Rodentia (6%), and the remaining came from a variety of taxonomic groups (Artiodactyla, Lagomorpha, Didelphimorphia, Cingulata, and Eulipotyphla). The most commonly tested rodents were beavers (*Castor canadensis*; n = 1,609), nutrias (*Myocastor coypus*; n = 204), and muskrats (*Ondatra zibethicus*; n = 94).”

Lines 505-506: It may not have a huge impact, but the IUCN range maps are not great representations of mammal species distributions. They can be wrong on a large scale, missing ranges by over 200 miles, but they are also not fine scale enough to capture elevational variation. My concern is that it could cause problems with the findings regarding higher risk at elevation. The elevation data are at a much finer scale than the rodent species distributions. There is no better source for mammal distributions for these types of analyses, but I think the authors should include a caveat about the quality of these data.

We appreciate this point and have added a relevant disclaimer, including a citation to work that supports this point:

“Rodent species richness was derived by stacking species IUCN expert range maps for the Rodentia, and rasterizing the richness layer using the *fasterize* package. IUCN maps are widely agreed to be unreliable at fine spatial scales for many species (Ramesh 2017), but in aggregate, are a suitable proxy for coarse gradients in richness.”

Supplemental Figures: It would be helpful to refer to Supplemental Table 1 for the variable abbreviations.

We have added “Variable abbreviations are explained in Supplementary Table 1.” to each figure caption as appropriate.